MULTIPLE SCLEROSIS
Update

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Disclosures

- I do not have any disclosures.

Multiple Sclerosis

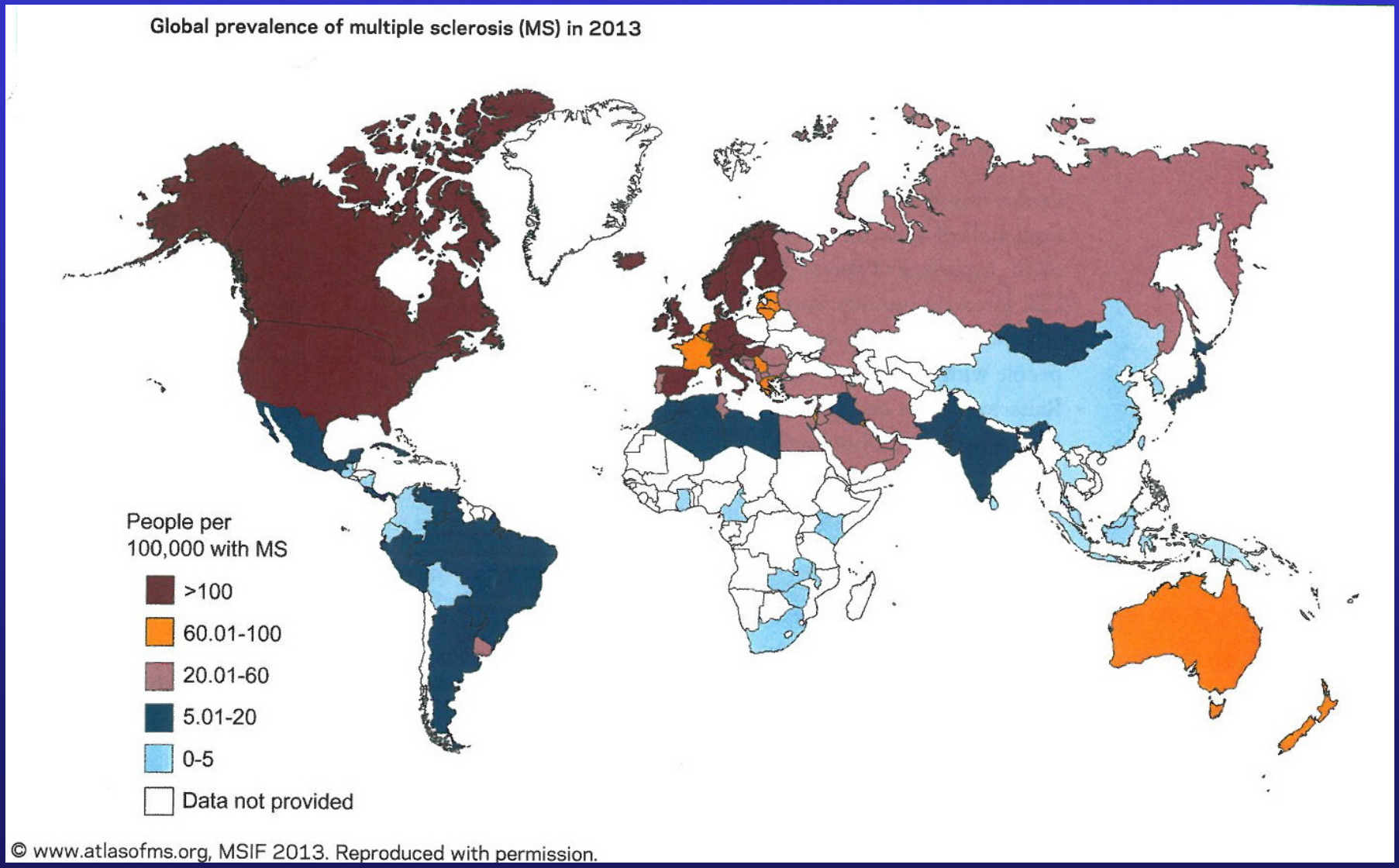
- Most common demyelinating disease of the CNS
  - > 90% affected prior to age 55
  - < 5% diagnosed before the age of 14
- Multifocal with lesions of different ages, time and site
- Relapsing and remitting (80%) vs progressive course (15%), focal single lesion (<5%)
- Classification:
  - Classic (Charcot type)
  - Acute (Marburg type)
  - Concentric sclerosis (Balo's type). Very rare
  - Schilder's disease – occurs in children, extensive demyelination, acute, can be remitting, responds to steroids.

Jean Martin Charcot (1825-1893)

Who gets MS?

1. National MS Society. *Just the Facts: 2006-2007.* Available at: www.nmss.org.
2. MS Network. *Who Gets MS?* Available at: www.ms-network.com.

MS: Magnitude of the Problem



Epidemiology of MS

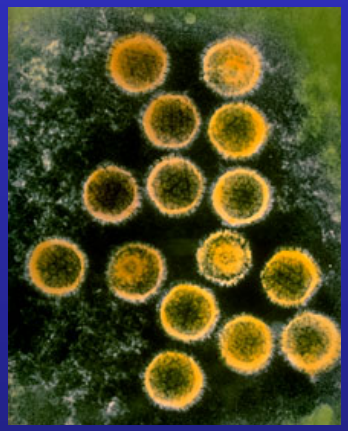
- Individuals who migrate to high risk area before age 10 have a high risk for disease
- Individuals who migrate to low risk area before age 10 assume a low risk for disease
- Individuals who migrate after the age of 10 assume the risk of the area in which they spent their first 10 years

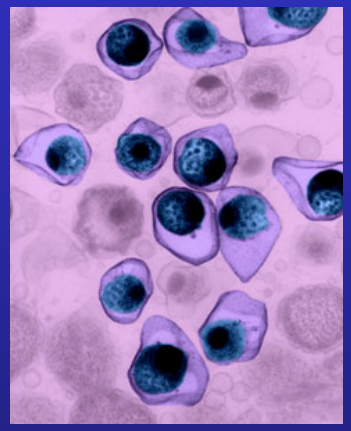
Birth Month and Risk of MS

- N = 17,874 Canadian patients with MS
- Significantly fewer patients with MS were born in November (p=.009) and more were born in May (p<0.0001) compared with other months
- Vitamin D influences the expression of HLA-DRB1*15

Willer CJ (*Br Med J* 2005)
Ramagopalan, S.V. (*AAN*, December 10, 2009)

Potential Triggers for Multiple Sclerosis





Genetic predisposition

Infectious agent → Abnormal immunologic response → MS

Environmental factors → Abnormal immunologic response → MS

MS = multiple sclerosis

Gilden DH *Lancet Neurol* 2005;4:195-202, Noseworthy et al. *N Engl J Med* 2000;343:938

Genetic Prevalence of MS

- In a recent genome wide transcription analysis for MS, 48 new genetic variants were identified

- Of interest most genes reverted back during pregnancy.

(Nature Genetics, September 2013)

Genetic Prevalence of MS

- 10 X increase for MS if direct relative affected
- Siblings of an affected person have a 2-5% risk of developing MS.
- Higher prevalence in identical twins
- Variability in severity of disease in twins and affected relatives

EBV and Children

- Children with MS demonstrate abnormally increased rates of EBV viral reactivation and a broader range of genetic variants, suggesting a selective impairment in their immunologic control of EBV.

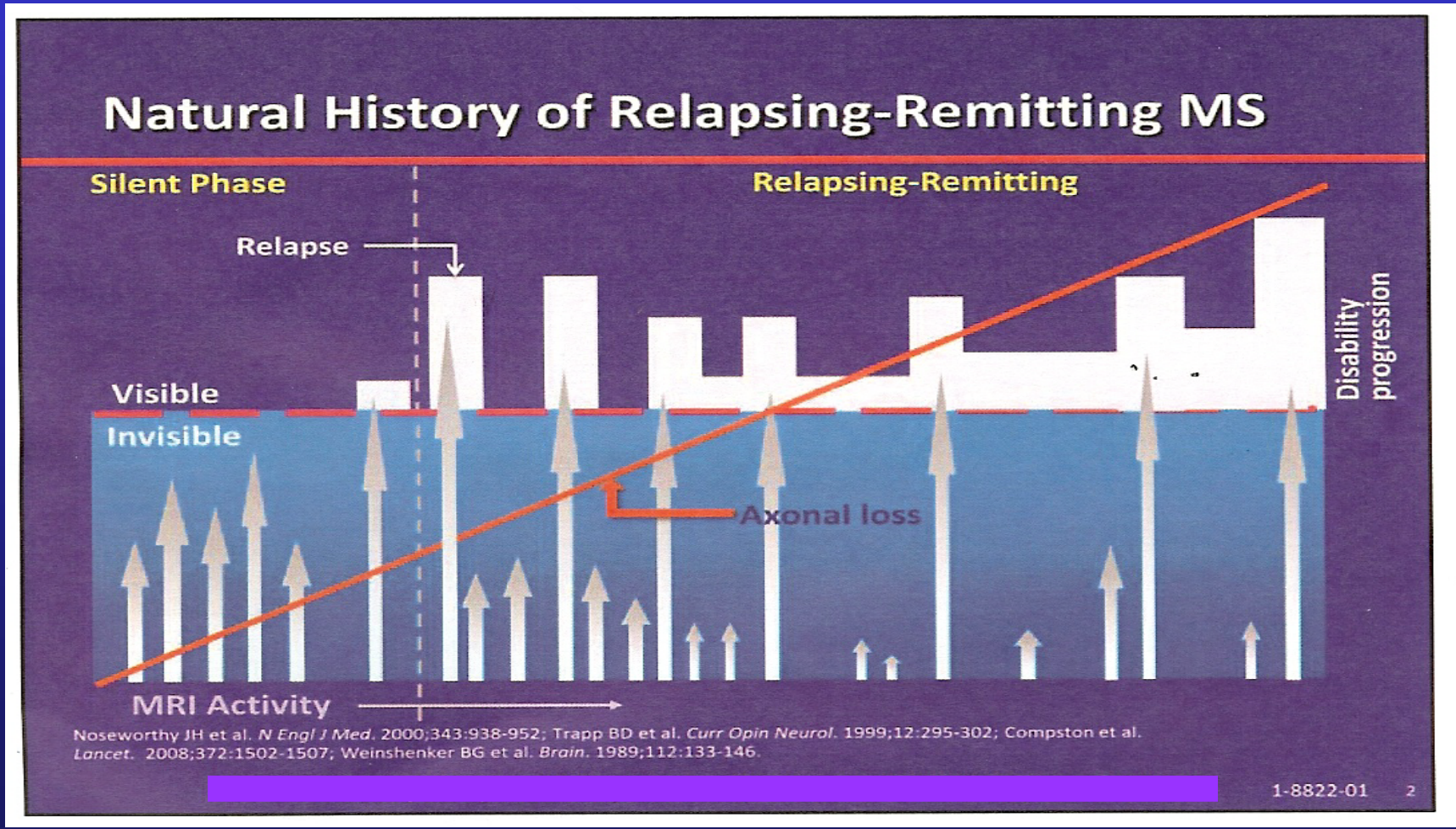
Yea, C (AAN, Oct 15, 2013)

Update on IM and MS

- Research on EBV has continued to evolve.
- Latest findings shows that it is unlikely any of the studied polymorphisms contribute to explaining association between anti-EBNA1 Ab titer or history of IM and MS.

Simon, KC (Multiple Sclerosis and Related Disorders, 2015)

Natural History of MS



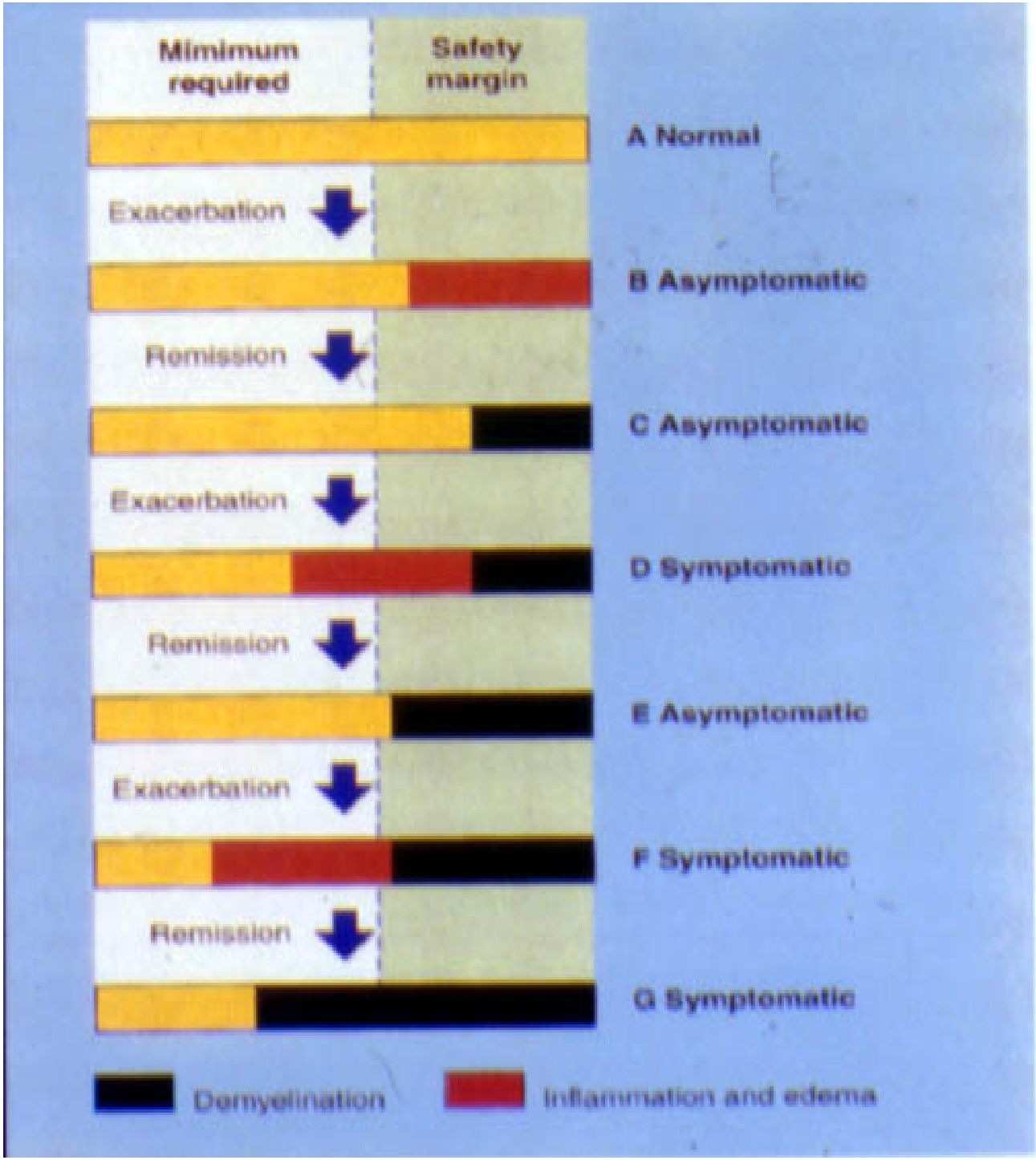
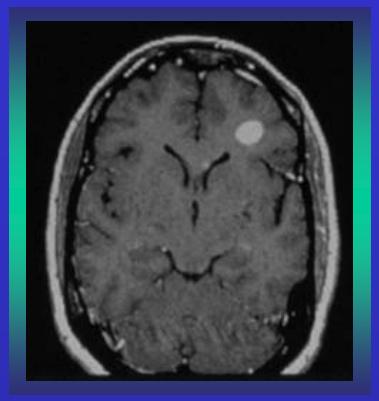
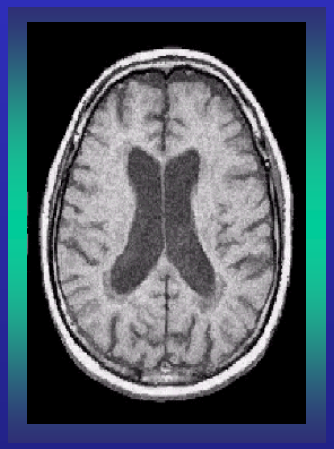


Figure 52 Safety factor in the progression of multiple sclerosis: As long as the required minimum number of nerve fibers remains intact, the patient is asymptomatic. When symptomatic myelin edema occurs during an exacerbation, remission may result in either complete or partial recovery, depending upon functional restoration of the required minimum number of fibers, or in a permanent deficit, as a result of myelinoclasia. From Poser, 1993; reproduced with the permission of Elsevier Science BV

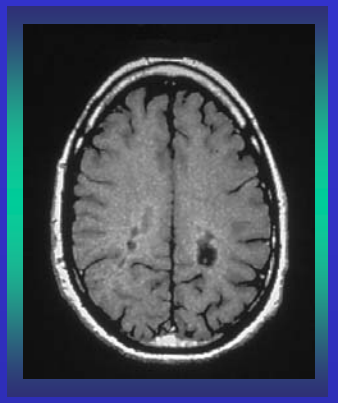
MR Imaging in MS



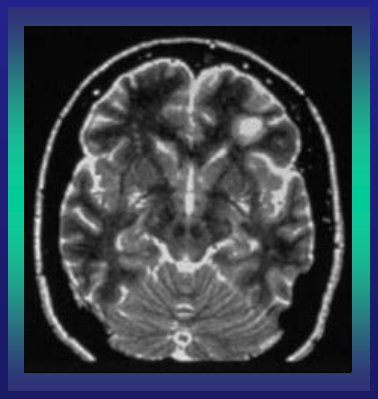
Gd enhancement



Brain atrophy (shrinkage)

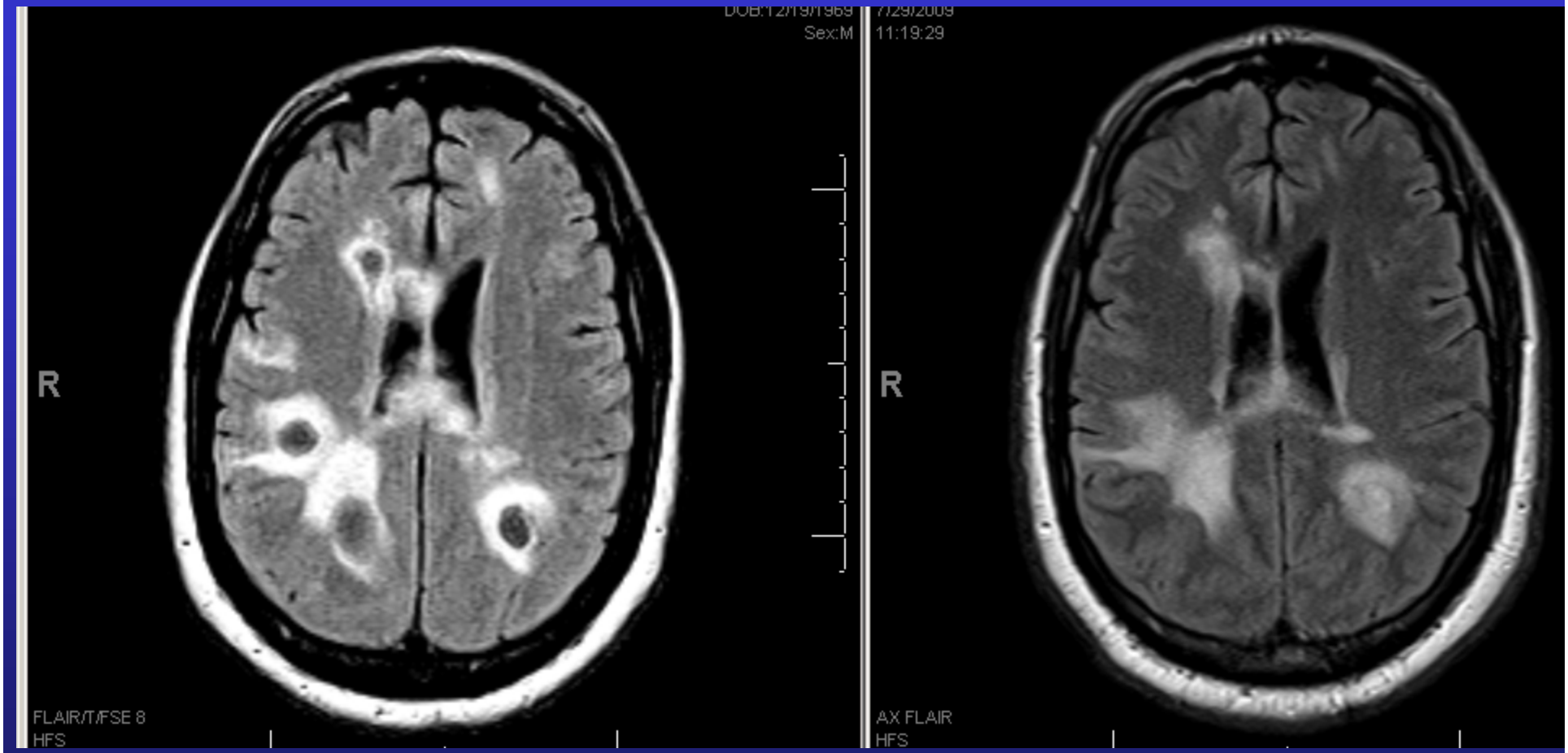


T1 “black hole”

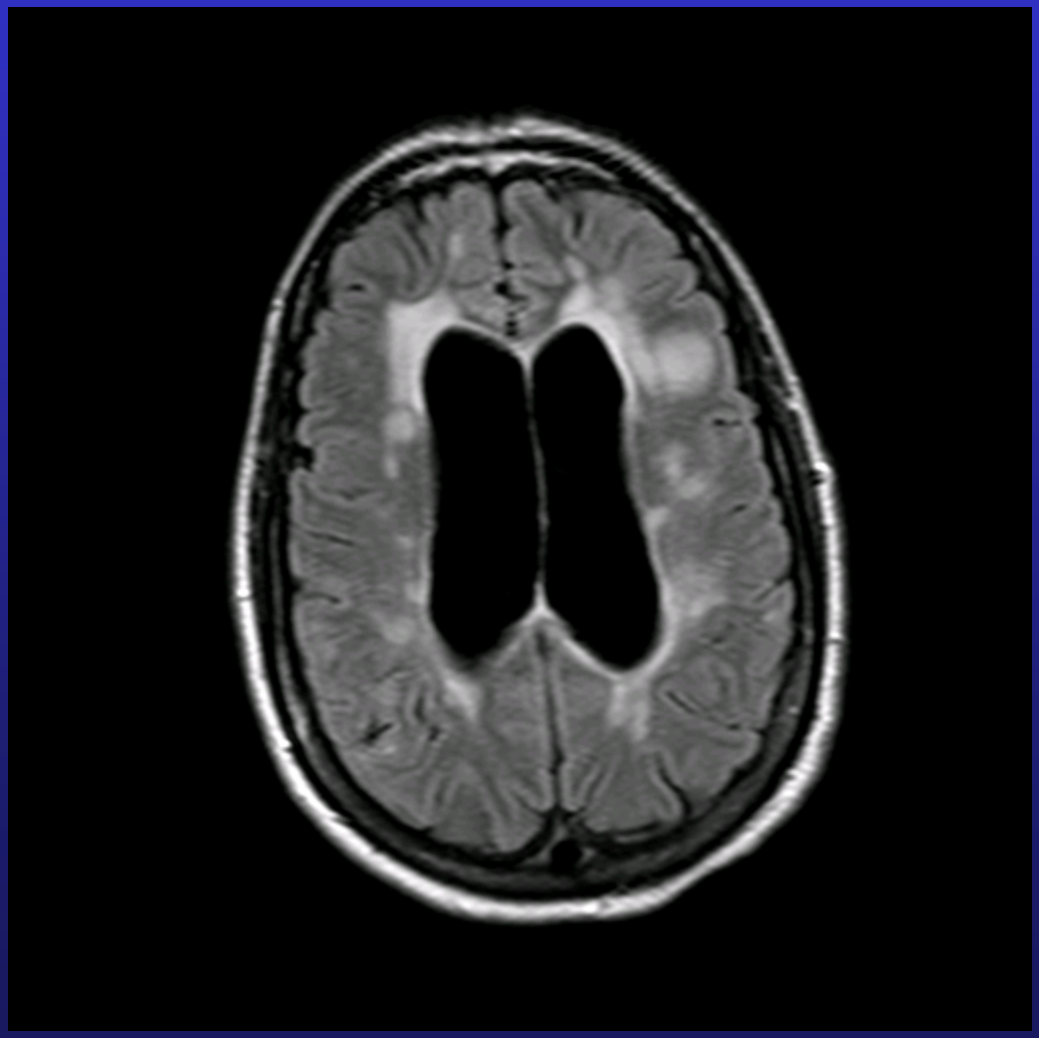


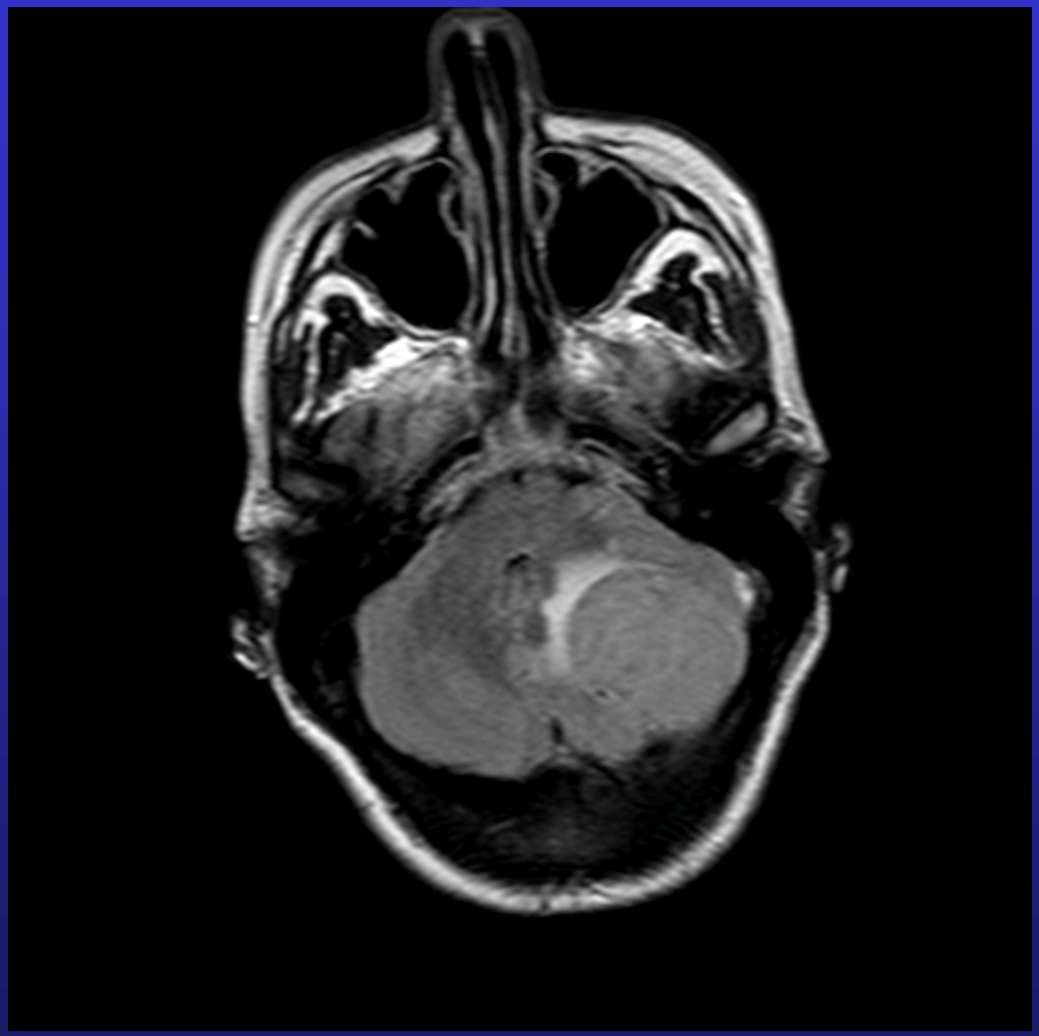
T2 lesion

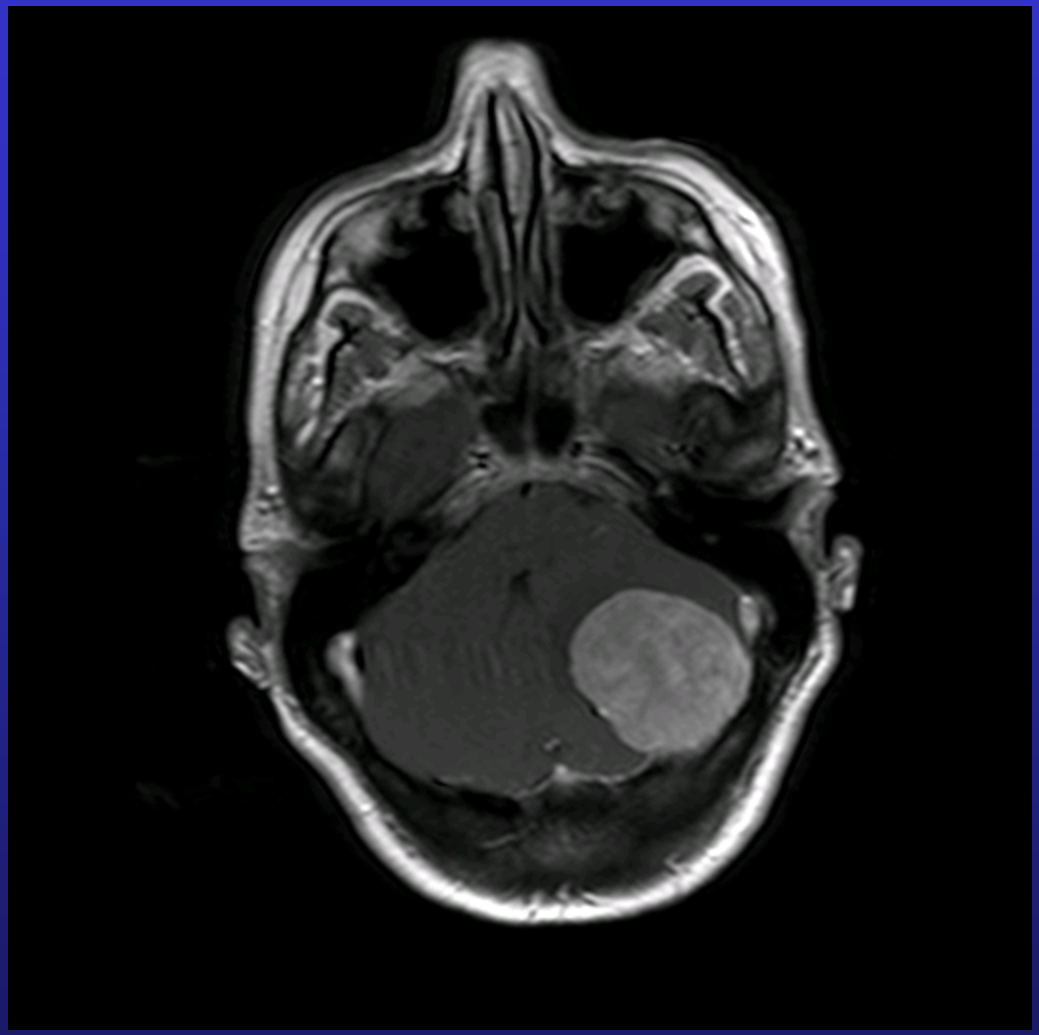
Spinal cord lesion

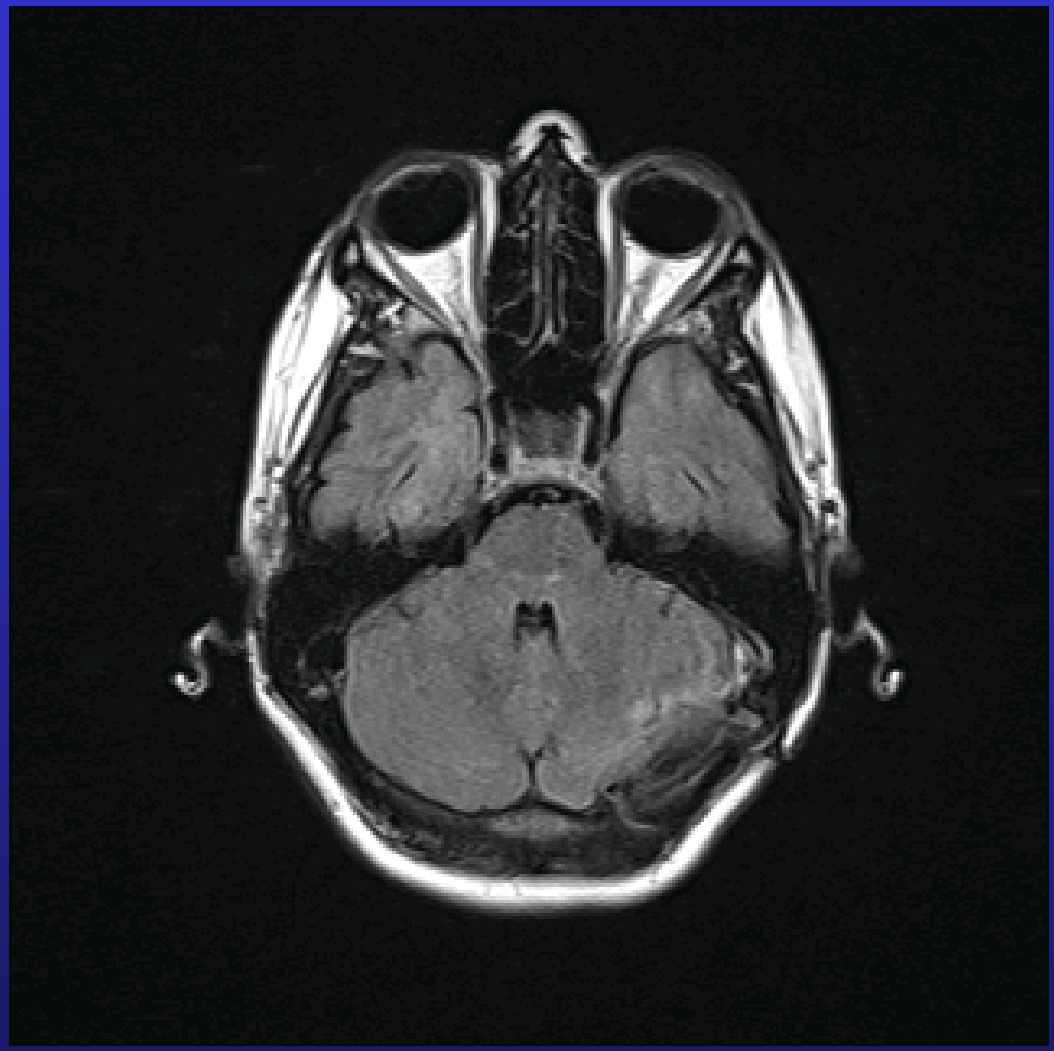


47 year old female; RN









MRI Findings in the Diagnosis of MS

MRI Findings Supporting the Diagnosis of MS	MRI Findings cautioning against the Diagnosis of MS
• Lesion size > 5 mm in diameter • Lesion shape – ovoid or oval • Lesion location – Periventricular, perivenular (Dawson's fingers), juxtacortical, corpus callosum, intratentorial, spinal cord • Homogeneous or open ring-enhancing • Presence of T1 black holes	• Lesion size smaller, many or all ≤ 5 mm in diameter • Lesion shape – linear, punctate, comma, subtle • Lesion location – lack of periventricular involvement • Meningeal/basilar enhancement • Normal scan of brain and spinal cord

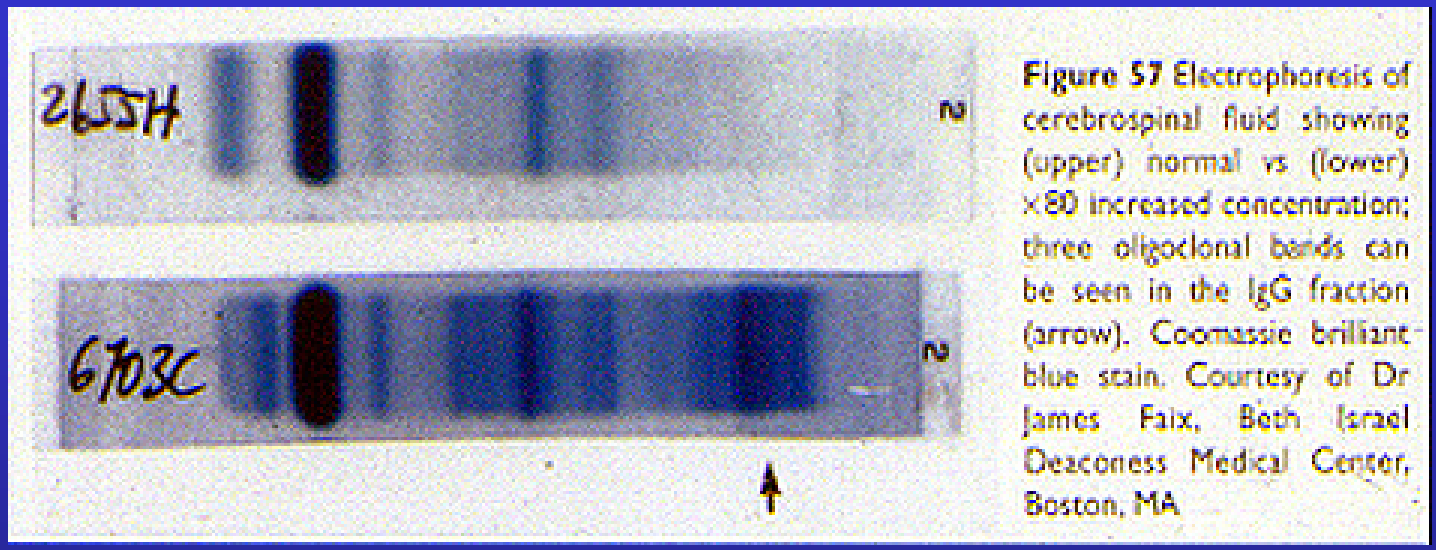
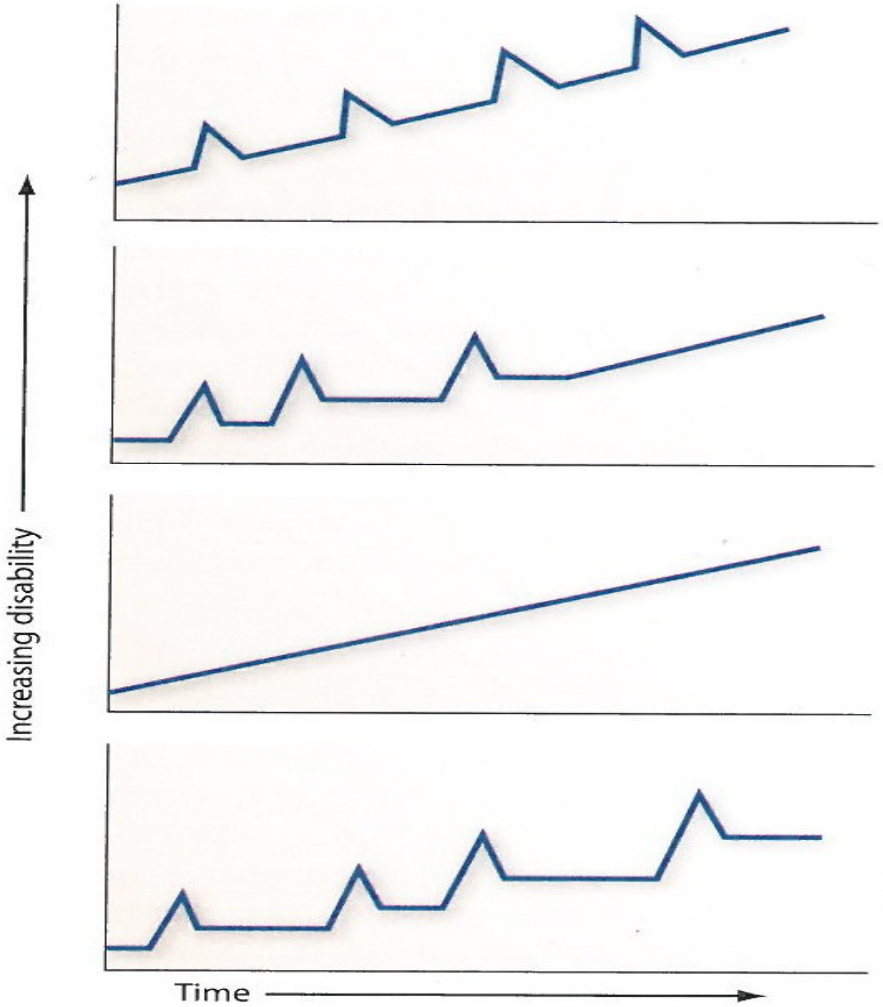


Figure 57 Electrophoresis of cerebrospinal fluid showing (upper) normal vs (lower) ×80 increased concentration; three oligoclonal bands can be seen in the IgG fraction (arrow). Coomassie brilliant blue stain. Courtesy of Dr James Faix, Beth Israel Deaconess Medical Center, Boston, MA

- Oligoclonal bands are more sensitive and specific (90-95%).
- IgG index or IgG synthesis are sensitive and specific (70-75%).

MS: Clinical Subtypes



Progressive-relapsing multiple sclerosis
Steady decline in function since onset, with superimposed attacks

Secondary progressive multiple sclerosis
Initial relapsing-remitting multiple sclerosis followed by a sudden decline in function, with periods of remission

Primary progressive multiple sclerosis
Steady increase in disability without attacks

Relapsing-remitting multiple sclerosis
Unpredictable attacks, which may or may not leave permanent deficits, followed by periods of remission

FIGURE 3 Types of multiple sclerosis. Adapted, with permission, from a slide presented by Anne Gocke, PhD, at the 2014 joint CMSC/ACTRIMS annual meeting.

Differential Diagnosis of MS

- Inflammatory diseases
  - SLE
  - Sjogren's disease
  - Behcet's disease
  - Polyarteritis nodosa
  - Granulomatous angitis
  - Sarcoidosis
  - Paraneoplastic encephalomyetopathies
- Infectious diseases
  - Lyme disease
  - HTLV-1
  - PML
  - HIV myelopathy/encephalopathy
  - Neurosyphilis
- Disease of myelin
  - ALD
  - ADEM
  - Central pontine myelinolysis
- Vascular
  - Lacunes
  - Embolic
  - CADASIL
  - Stroke due to APLA
- Miscellaneous
  - Spinocerebellar disorders
  - Cervical spondylosis
  - Arnold-Chiari malformation
  - Syrinx
  - Vitamin B12 deficiency
  - Hashimoto Thyroiditis
  - Leber's Optic Atrophy

Clinical Presentations of MS

Multiple Sclerosis: Common Symptoms

Symptom	Prevalence, %
Bladder symptoms	90
Fatigue	80
Spasticity	70
Sexual dysfunction	64
Pain	62
Cognitive dysfunction	50 in 15 yrs, 90 in 25 yrs
Depression	50
Bowel dysfunction	40

Goodin et al. *Mult Scler.* 1999; 5:78-88.

Fatigue in MS

- Probably the single most common symptom shared by patients with MS
  - Reported > 75% of patients
  - In 30% of patients, it occurs before other symptoms of the disease
- In many patients, fatigue is the most disabling symptom and one of the most common reasons for retirement due to disability

Depression and Multiple Sclerosis

- Does MS cause depression?
- Does the therapy for MS (specifically IFN) cause depression?
- How is depression best managed?

Cognitive Impairment in Untreated MS

- Occurs in approximately half of all people with MS
- Often under recognized or misdiagnosed as depression, stress, or personality disorder
- Impairs daily functioning of people with MS
- Leading cause of unemployment in persons with MS

Currently Approved Disease-Modifying Therapies for Patients with Relapsing-Remitting Multiple Sclerosis

Year	Generic name (trade name)	Route and frequency of administration
1993	Interferon β-1b (Betaseron)	Subcutaneous injection every other day
1996	Interferon β-1a (Avonex)	Intramuscular injection once a week
1996	Glatiramer acetate (Copaxone)	Subcutaneous injection once a day
2000	Mitoxantrone (Novantrone)	Intravenous infusion every 3 months
2002	Interferon β-1a (Rebif)	Subcutaneous injection 3 times a week
2004	Natalizumab (Tysabri)	Intravenous infusion once a month
2009	Interferon β-1b (Extavia)	Subcutaneous injection every other day
2010	Fingolimod (Gilenya)	Orally once a day
2012	Teriflunomide (Aubagio)	Orally once a day
2013	Dimethyl fumarate (Tecfidera)	Orally twice a day
2014	Glatiramer acetate (Copaxone)	Subcutaneous injection 3 times a week
2014	Peginterferon β-1a (Plegridy)	Subcutaneous injection every 14 days

(ACTRIMS, Summer 2014)

Mesenchymal Stem Cells as a Treatment for MS

- Mesenchymal stem cells (MSCs) could reduce inflammatory lesions in patients with MS.
- MSCs can be derived from bone marrow or placenta.

(Neurology Reviews, July 2013)

Complementary & Alternative Medicine in MS

- The guidelines demonstrate that even though there are multiple CAM therapies, there is little evidence that most of them are effectively treating MS.

(Neurology Today, 2014)

- Functional brain abnormalities linked to cognitive impairments in MS patients who use Marijuana

- Medical Marijuana does not appear to have curative effects on any neurologic condition, but it may ameliorate unwanted symptoms and ease suffering.

Hurley (Neurology Today, 2014)
Fife (AAN, 2015)

Vitamin D

- Vitamin D is a protective factor in MS
- For every 10 ng/mL increase in Vitamin D levels in patients with MS, their EDSS scores were 0.05 points lower.
- Recommended Vitamin D levels of 50-80 ng/mL.

Otto, A (Clinical Neurology News, June 2012)

Additional CAM Therapies

- Ginkgo biloba
- Ginseng
- Omega-3 fatty acid (anti-inflammatory)
- Omega-6 fatty acid (pro-inflammatory)

Medical Management During Pregnancy, Delivery, and Postpartum

- None of the disease-modifying medications are approved for use during pregnancy.
- The disease-modifying drugs are also not recommended for use during breastfeeding.
- Women with MS usually do not need special gynecologic care during pregnancy, labor and delivery.

Conclusion

- MS is the most common demyelinating disease of the CNS.
- Relapsing remitting (80%), Progressive (15%), Focal Single Lesion (< 5%)
- 200 Americans (primary between ages 20-50) diagnosed weekly with MS.
- More than twice as many women have MS than men.
- Less than 10% of all MS patients are younger than age 18.
- 10% increase for MS if direct relative affected.

Conclusion (con't)

- Correlation between EBNA-1 IgG and gadolinium enhancing lesions in MS disease activity.
- Patients need to undergo an MRI and CSF for oligoclonal bands and IgG index/synthesis.
- Diagnosing MS is still a clinical diagnosis (no single diagnostic laboratory test).

Conclusion (con't)

- Common symptoms include neurogenic bladder, fatigue, spasticity, sexual dysfunction, pain, cognitive dysfunction, and depression.
- There are several different types of injectable and oral medications for treatment.

Take Home Message

Patients do not care about how much you know. What they want to know is how much you care!

Thank you!

Q & A